

## REMARKS

Claims 71-134 are pending.

Applicants elect with traverse Group II (claims 90-126 and 132-133) for examination on the merits. There would be no serious burden if all claims were examined in this application. The claim amendment is supported by the original disclosure and does not add new matter. It corrects an informality and does not affect the scope of the claims. Applicants reserve the right to prosecute the non-elected subject matter in a further patent application. Further, under the Notice dated March 26, 1996 (1184 OG 86), Applicants request rejoinder of the non-elected method claims upon an indication that an elected product claim is allowable.

In satisfaction of their duties of candor and good faith, Applicants bring to the attention of the Examiner the related subject matter in Application Nos. 09/738,879, 09/950,003, 10/240,606, 10/274,706, 10/484,883, 10/496,037, 10/518,229, 10/518,303, 10/582,687, 10/868,359, 10/902,285, 11/030,156 and 11/440,749. She is invited to consider their prosecution histories in this application. The file wrappers of most, if not all, of these applications are accessible electronically so resubmission of those papers here would be redundant. But, if the Examiner prefers, Applicants would resubmit them in this application.

It was alleged by the Examiner that the special technical feature linking Groups I and II is an epiK5-N,O-oversulfate derivative, and that there is a lack of unity because "Oreste et al. (US 2002/0062019) teach a C5-epimerized N,O-sulfate K5 glycosaminoglycan which is submitted to nitrous acid depolymerization" at page 2 of the Office Action. But the epiK5-N,O-oversulfate derivative requires "a sulfation degree of at least 4" according to the definition on page 7, lines 6-7, of Applicants' specification. There is unity of invention because Oreste et al. (the '019 application) teach a C5-epimerized N,O-sulfate K5 glycosaminoglycan ("epiK5-N,O-sulfate" according to Applicants' present nomenclature) that is not, and cannot be, an epiK5-N,O-oversulfate. The evidence cited by the Examiner in the Office Action does not anticipate or render obvious the special technical feature shared by the pending claims. Further, methods of making and using

the elected products should be examined in the same application because it was filed under 35 U.S.C. 371.

Oreste et al. (the '019 application) prepare epiK5-N,O-sulfate according to a process comprising:

- (i) N-deacetylation and N-sulfation of K5 polysaccharide to provide a K5-N-sulfate,
- (ii) C5-epimerization to provide an epiK5-N-sulfate,
- (iii) preparation of a ternary or quaternary salt of the epiK5-N-sulfate and oversulfation of the salt to provide an epiK5-amine-O-oversulfate,
- (iv) O-desulfation of the epiK5-amine-O-oversulfate,
- (v) selective 6-O-sulfation of the epiK5-amine-(partially)O-desulfate, and
- (vi) N-sulfation.

The epiK5-N,O-sulfates made according to the above process have the structure I and a degree of sulfation of from 2.3 to 2.9 (see paragraphs [0138]-[0146] of the '019 application). They have several anti-coagulant properties (see paragraph [0170] of the '019 application).

The pending claims require the core structure (A), which is shown on page 3 of the present specification, that was modified by removal of an N-acetyl group and addition of an N-sulfate group by partial C5-epimerization to provide an epiK5-N-sulfate. This process is described in detail in Applicants' specification. Starting from the epiK5-N-sulfate, all of the compounds claimed in this application can be prepared according to an inventive concept directed to the preparation of epiK5-N,O-oversulfates having a molecular weight of from 2,000 to 45,000 and a sulfation degree higher than 4 by three simple reactions: (a) preparation of a ternary or quaternary salt of the optionally depolymerized epiK5-N-sulfate under conditions not disclosed in step (iii) of Oreste et al. (the '019 application), (b) oversulfation of the salt to provide an epiK5-amine-O-oversulfate having a high degree of sulfation (in particular 3.55 to 3.8) not obtainable according to step (iii) of Oreste et al. (the '019 application), and (3) N-sulfation thereof to provide novel and non-obvious epiK5-N,O-sulfate derivatives. These epiK5-N,O-oversulfates have a degree of sulfation of at least 4 and are basically inactive in coagulation (see page 29, lines 21-23, of the present specification).

In summary, the processes are different, the structures of the compounds are different, and the biological properties of the compounds are different:

- step (a) is novel and is carried out under conditions that are neither taught nor rendered obvious by Oreste et al. (the '019 application), those conditions allow the preparation of novel epiK5-amine-O-oversulfate derivatives having a degree of sulfation (in particular 3.55 to 3.8) never attained before;
- step (b) is carried out under known conditions but, as set forth above, provides novel epiK5-amine-O-oversulfate derivatives neither taught nor rendered obvious by Oreste et al. (the '019 application);
- step (c) is also novel, although carried out under known conditions, because direct N-sulfation of an epiK5-amine-O-oversulfate derivative was not described before the effective filing date of this application, and such N-sulfation provides novel epiK5-N,O-oversulfates having a high degree of sulfation (at least 4) never before attained;
- epiK5-N,O-sulfate derivatives obtainable by Oreste et al. (the '019 application) and epiK5-N,O-sulfate derivatives obtainable according to the present invention have different properties: anti-coagulant and anti-thrombotic activities for the prior art versus anti-angiogenic and anti-viral activities (and basically inactive in coagulation) for the inventive compounds, respectively (see page 8, line 28, to page 9, line 8, of the present specification).

The technical feature shared by all of the pending claims is completely different, in many aspects, from the prior art. The evidence of record thus does not establish a lack of unity. Further, the subject matter of the pending claims is so closely related that a search and examination of the entire application could be made by the Examiner without serious burden. Finally, Groups I-IV are closely linked each other by a "starting material-intermediate-final product" relationship in a new and non-obvious process of manufacture.

Applicants earnestly solicit an early and favorable examination on the merits. The Examiner is invited to contact the undersigned if any further information is required.

Respectfully submitted,

**NIXON & VANDERHYE P.C.**

By:                     /Gary R. Tanigawa/                    

Gary R. Tanigawa

Reg. No. 43,180

901 North Glebe Road, 11th Floor  
Arlington, VA 22203-1808  
Telephone: (703) 816-4000  
Facsimile: (703) 816-4100